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Inherited Metabolic Disorders Involving the Nervous System

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Inherited metabolic disorders (IMD) are a group of disorders caused by defects in specific biochemical pathways. Up to 85% of IMD display predominantly neurological manifestations by affecting neurodevelopment or causing neurodegeneration. These neurometabolic disorders present with a variety of neurological and non-neurological manifestations. Early diagnosis of IMD is important because some disorders can be treated or improved with specific treatment if detected early. For prompt diagnosis and treatment, it is important to suspect IMD by being familiar with the clinical characteristics, biochemical abnormalities, and characteristic neuroimaging patterns that appear in IMD. Genetic testing, including next-generation sequencing, is also important in diagnosing IMD. During the follow-up of patients with IMD, it is necessary to conduct regular physical and neurological examinations in addition to disease-specific management.

Key words: Inherited metabolic disorders, Neurometabolic, Clinical, Biochemical, Neuroimaging, Genetic testing

Introduction

Inherited metabolic disorders (IMD) are a group of disorders caused by defects in specific biochemical pathways. They collectively represent one of the most common groups of single gene disorders although each is rare or very rare[1,2].

Many IMD are caused by deficiencies of enzymes, cofactors, or transporters required for specific metabolic pathways, resulting in deficiency of essential metabolites, accumulation of toxic metabolites/substances, and energy deficiency and subsequent damage to specific organs or organelles[1-3].

Up to 85% of IMD display predominantly neurological manifestations by affecting neurodevelopment or causing neurodegeneration[1]. Neurometabolic disorders (NMD) are characterized by mental or motor dysfunctions which include acute encephalopathy, epilepsy, movement disorder, developmental delay, abnormal head size, psychiatric symptoms, and congenital malformations of brain[3-7].

Most IMD occur in newborns and infants, although late onset IMD also exist[8]. It is important to consider IMD as a differential diagnosis when managing patients with neurological dysfunction.

An overview of NMD is reviewed, focusing on clinical manifestations, diagnostic approaches, and treatment.

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Clinical manifestations

A variety of clinical manifestations, including neurological and non-neurological manifestations, may appear in IMD due to multiple pathogenic mechanisms.

1. Neurological manifestations

Neurological manifestations are highly variable and may present as acute encephalopathy and subacute or slowly progressive symptoms. Epilepsy, hypotonia or spasticity, movement disorder, developmental delay or regression, intellectual disability, abnormal head size, stroke or stroke-like episodes, behavioral or psychiatric symptoms, and congenital malformations of the central nervous system may occur as neurological symptoms in IMD (Table 1)[3,7,9,10].

1) Epilepsy

Although IMD is a rare cause of epilepsy, seizure develops frequently in patients with IMD. Seizure may be the first and main symptom of IMD, as pyridoxine dependent epilepsy (PDE) in newborns[11]. Metabolic epilepsy can occur at any age and often has preceding symptoms, such as decreased level of consciousness, ataxia or dystonia, developmental delay or regression, and behavioral or psychiatric symptoms. It may also be accompanied by non-neurological signs, such as heart, kidney, and liver involvement, hearing or vision impairment, and hair or skin problems[11]. Epilepsy in NMD can be classified according to age of onset, pathogenic mechanism, and type of presenting seizure or epilepsy syndrome[11-12].

In neonatal seizure, NMD should be suspected as an underlying cause when the seizure is refractory to conventional anti-seizure medications and is associated with metabolic decompensation during concurrent fever or infections. Family history of neonatal death or neurological disease, maternal history of pregnancy with hemolysis elevated liver enzymes and low platelets (HELLP) syndrome or excessive fetal movements, rapid progression of encephalopathy, severe metabolic acidosis, or hiccups may be clues to the presence of IMD[13]. Representative IMD that manifest as metabolic epilepsy in newborns or early infants include PDE, pyridoxal 5'-phosphate oxidase (PNPO) deficiency, folinic-acid responsive seizure, biotinidase deficiency, glucose transporter 1 (GLUT1) deficiency, serine biosynthesis defects, molybdenum cofactor deficiency, sulfite oxidase deficiency, Menkes disease, nonketotic hyperglycinemia, disorders of peroxisome biogenesis and β-oxidation, congenital disorders of glycosylation, and congenital and early infantile neuronal ceroid lipofuscinosis (NCL)[11,12].

Metabolic epilepsy occur due to electrolyte imbalance, hyperammonemia, hypoglycemia or lack of brain energy, accumulation of neurotoxic metabolites/substances, deficiency of vitamins, cofactors, or nutrients, disturbances of neurotransmitter systems, accumulation or deficiency of metals/minerals, or associated brain malformations (Table 2)[3,12,14-16].

Seizure patterns may vary, but myoclonic seizure is common. Progressive myoclonic epilepsy, infantile spasm, epilepsia partialis continua or refractory myoclonic or tonic seizure with a burst suppression pattern on electroencephalogram may be suggestive findings of IMD. A family history of epilepsy, intellectual disability or cognitive decline, other neurological abnormalities, involvement of other organs, and seizures occurring after fasting or eating certain foods can be clues to metabolic epilepsy at any age[14-17].

2) Mimics of cerebral palsy

A large number of IMD can present with cerebral palsy (CP)-like symptoms including dystonia, spasticity, upper motor neuron signs, abnormal gait, ataxia, or hypotonia, as 'CP mimics'[18]. Spastic paraplegia is one of the most common 'CP mimics' in IMD[19]. Although

patients with IMD may present with symptoms and signs similar to CP, advances in comprehensive metabolic and genetic investigations are increasing the number of cases in which NMD is being identified as the underlying cause. A detailed history taking and careful physical and neurological examination are essential when evaluating a patient with suspected CP. The possibility of mimicking CP should be considered when CP symptoms appear in the absence of a history of risk factors that lead to brain injury, such as preterm birth, hypoxic-ischemic injury, intracranial hemorrhage, kernicterus, cerebrovascular accident, or head injury.

Table 1. Neurological symptoms in inherited metabolic disorders[3,7,9,10,32,36]

Neurological symptoms	Inherited metabolic disorders
Acute encephalopathy	Organic acidurias, Disorders of amino acid netabolism, Urea cycle defects, Fatty acid oxidation defects, Primary lactic acidosis, Nonketotic hyperglycinemia, Molybdenum cofactor deficiency, Sulfite oxidase deficiency
Epilepsy	GLUT1 deficiency, PDE, Pyridoxal 5'-phosphate responsive epilepsy, Folinic acid responsive epilepsy, Serine synthesis defect, Nonketotic hyperglycinemia, Peroxisomal disorder, Sulfite oxidase deficiency, Molybdenum cofactor deficiency, Respiratory chain disorders, Menkes disease, Mitochondrial disorders, NCL, Metal metabolism disorders, Cerebral creatine deficiency syndromes
Mimics of cerebral palsy	Hypotonia: Congenital lactic acidosis, Peroxisomal disorders, Nonketotic hyperglycinemia, Urea cycle defects, Sulfite oxidase deficiency, Lowe syndrome, Pompe disease, Primary carnitine deficiency, Fatty acid oxidation defects, Primary coenzyme Q10 deficiency, Neurotransmitter deficiency Spasticity: Sulfite oxidase deficiency, Hyperornithinemia, hyperammonemia, homocitrullinuria (HHH syndrome), Arginase deficiency, Homocysteine remethylation defects, Adrenoleukodystrophy, Krabbe disease, Canavan disease, Metachromatic leukodystrophy
Movement disorder	Neurotransmitter defects, Cerebral creatine deficiency syndromes, Leigh disease, Lesch-Nyhan syndrome, Glutaric aciduria type 1, Biotin thiamine responsive basal ganglia disease, Cerebral folate deficiency, GLUT1 deficiency, Wilson disease, Manganese transporter deficiency, Late onset GM1 gangliosidosis, Maple syrup urine disease, Nonnketotic hyperglycinemia, Methylmalonic acidemia, Galactosemia, Mitochondrial diseases
Eye movement disorder	External ophthalmoplegia: Mitochondrial disorders, Biotin thiamine responsive basal ganglia disease Gaze palsy: Niemann-Pick type C, Gaucher disease Oculogyric crisis: Disorders of dopamine synthesis
Developmental delay, regression, intellectual disability	HHH syndrome, Late onset nonketotic hyperglycinemia, Phenylketonuria, Cerebrotendinous xanthomatosis, GLUT1 syndrome, Hyperinsulinism hyperammonemia syndrome, Homocystinuria, Wilson disease, Coenzyme Q10 defciency, Biotinidase deficiency, Peroxisomal disorder, Neurotransmitter deficiency
Abnormal head size	Microcephaly: GLUT1 deficiency, Menkes disease, Sulfite oxidase deficiency, Molybdenum cofactor deficiency, Amino acid synthesis disorders (serine, asparagine, and glutamine synthetase deficiencies), Methylene tetrahydrofolate reductase deficiency Macrocephaly: Alexander disease, Canavan disease, Glutaric aciduria type 1, L2-hydroxyglutaric aciduria, Megalencephalic leukoencephalopathy with subcortical cysts, Tay-Sachs disease
Stroke	Homocystinuria, Fabry disease
Stroke like episodes	Urea cycle defects, MELAS, Methylmalonic acidemia, Propionic acidemia, Isovaleric aciduria, Congenital disorders of glycosylation
Behavioral or psychiatric manifestations	Urea cycle disorder, Homocystinuria, Smith-Lemli-Opitz syndrome, Cerebral creatine deficiency syndromes, Porphyrias, Lesch-Nyhan syndrome, Phenylketonuria, Sanfilippo syndrome, Wilson disease, Niemann-Pick type C, Juvenile/adult onset metachromatic leukodystrophy, Cobalamin C disease, Late onset GM2 gangliosidosis
Congenital malformations of the central nervous system	Zellweger syndrome, Pyruvate dehydrogenase deficiency, Smith-Lemli-Opitz syndrome, Nonketotic hyperglycinemia, Sulfite oxidase deficiency

The presence of family members with similar symptoms, progressiveness of neurological symptoms, regression of milestones, diurnal changes or fluctuations in symptoms related to activity, fasting, or eating, unusual appearance, abnormalities in eye movements, optic atrophy, or retinopathy may be a finding suggestive of IMD which can show similar symptoms to CP[18-20].

3) Movement disorder

Movement disorders (MD) are one of the important neurological manifestations of IMD resulting from central nervous system or selective basal ganglia involvement[21]. The basal ganglia are particularly vulnerable to certain NMD, including energy metabolism defects, lysosomal storage disorders, and metal metabolism disorders[21-28]. MD associated with IMD may manifest as more than one type of MD, evolve over time, and is usually associated with additional neurological features, resulting in complex clinical presentations. IMD should be considered as the underlying etiology when MD is not explained by typical disorders such as structural brain lesions, infectious or autoimmune encephalitis, toxic or drug-induced diseases, or other genetic or neurodegenerative diseases[21].

Hyperkinetic movements include ataxia, dystonia, chorea, athetosis, myoclonus, tremor, tics, and stereotypy, and hypokinetic movements include bradykinesia, hypokinesia, and hypokinetic-rigid syndrome[5]. Ataxia and dystonia are common in IMD. It is recommended to suspect IMD when ataxia is accompanied by other neurological symptoms, characteristic facial features, and other types of MD[21-28]. The earlier ataxia occurs, the more likely it is to be caused by IMD. Ataxia can occur in a variety of IMD which include congenital disorders of amino acid metabolism, peroxisomal disorders, organic acidemia, mitochondrial diseases, lysosomal storage disorders, or congenital disorders of glycosylation[22-26].

Dystonia also occurs in a wide range of IMD[25]. Various types of MD can occur with seizure, abnormal eye movement, hearing impairment, organomegaly, and skin problems. Dystonia related with IMD usually have a generalized distribution and present at a young age with an acute onset following metabolic decompensation affected by illness, fatigue, exercise, fasting, or eating certain foods[25-27]. Insidious and progressive clinical courses may also be observed.

Oculomotor disorders are frequently observed in lysosomal storage disorders or mitochondrial diseases. Oculogyric crisis is an important feature of disorders of dopamine synthesis or transport[28,29].

4) Developmental delay, regression, or intellectual disability

IMD is a rare cause of developmental delay or intellectual disability[7,30,31]. Family history of consanguinity, unexplained neonatal or infantile death, maternal history of acute fatty liver of pregnancy (AFLP) or HELLP syndrome, past medical history of unexplained hypoglycemia or encephalopathy are clues to IMD as a possible cause of developmental delay or intellectual disability[7]. Typical facial features, self-injurious behavior, psychiatric symptoms, seizure, hypotonia, regression, hepatosplenomegaly, cardiomyopathy, dystonia, abnormal head size, growth failure, kinky hair, or eczema may appear according to the specific IMD[7].

5) Abnormal head size

Microcephaly or macrocephaly may occur in a variety of IMD[3,32]. Disruption of metabolic pathways at an early stage can affect brain development or cause neurodegeneration, leading to microcephaly. Smith-Lemli-Opitz syndrome, GLUT1 deficiency, Menkes disease, cerebral folate deficiency, sulfite oxidase deficiency, molybdenum cofactor deficiency, amino acid synthesis disorders (serine, asparagine, and glutamine synthetase deficiencies), and methylene tetrahydrofolate reductase deficiency are representative IMD that cause

microcephaly[32]. Macrocephaly may be found in Alexander disease, Canavan disease, Glutaric aciduria type 1, and L2-hydroxyglutaric aciduria[3].

6) Stroke or stroke-like episode (SLE)

Stroke or stroke-like episode (SLE) may occur in many IMD. SLEs are dominant phenotypic features of various mitochondrial disorders, especially in mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes syndrome (MELAS)[33]. SLEs may occur in Leigh syndrome, Kearns-Sayre syndrome, myoclonus epilepsy with ragged red fibers syndrome (MERRF), urea cycle disorders, organic acidemias (methylmalonic acidemia, propionic acidemia, isovaleric aciduria), lysosomal storage disease, congenital disorders of glycosylation, and succinic semialdehyde dehydrogenase deficiency[33].

7) Behavioral or psychiatric symptoms

A variety of psychiatric symptoms such as depression, anxiety disorder, psychosis, attention deficit hyperactivity disorder, autism spectrum disorder, bipolar disorder and obsessive-compulsive disorder may occur in IMD[34]. Wilson disease, mitochondrial disorders, pheylketonuria, homocystinuria, cobalamin C disorder, urea cycle defects, Niemann-Pick disease type C are examples of NMD that present with psychiatric symptoms[34,35].

8) Congenital malformations of the central nervous system

NMD can cause disruptions in brain development because metabolic and developmental pathways are tightly linked and interact with each other. Brain malformations such as absence or hypoplasia of the corpus callosum, midline brain defects, and malformations of the cortex, cerebellum, and brainstem may be associated with IMD. A variety of pathogenic mechanisms including energy deficiency and defects in cellular respiration, essential nutrient deficiencies, accumulation of neurotoxic metabolites, defects in cell signaling pathways, altered biophysical properties of cell membranes, and dysfunction of intracellular organelles may be involved (Table 2)[36].

2. Non-neurological manifestations

Vomiting, poor weight gain, cardiomyopathy, hepatosplenomegaly, kidney disease, ophthalmologic problems, skin or hair manifestations may be associated with many NMD[5,7,8]. Cornel clouding, cataract, Kayser-Fleischer ring, lens dislocation, retinitis pigmentosa, cherry red spots, and optic nerve atrophy may occur in IMD[37]. Alopecia, trichorrhexis nodosa, kinky hair, eczema, erosive exfoliative dermatitis, hyperpigmentation, hypopigmentation, scleroderma, photosensitivity, and congenital ichthyosis may occur in IMD[3].

Diagnostic approaches

Early diagnosis of IMD is crucial for appropriate treatment in order to prevent metabolic decompensation and minimize brain damage, especially for treatable NMD. It is also useful to inform accurate counselling on prognosis and risk of recurrence[1-3,13]. For this, it is important to suspect the possibility of IMD when managing patients with neurological dysfunction. Many NMD present diagnostic challenges because clinical presentations and radiological abnormalities vary and sometimes overlap depending on the stage of the disease. However, there may be clinical clues, biochemical features, and characteristic neuroimaging patterns suggestive of IMD. Therefore, a systematic approach based on a detailed review of clinical symptoms and signs, biochemical investigations, neuroimaging studies, and genetic studies is recommended for the diagnosis of NMD (Fig. 1).

Table 2. Classification of inherited metabolic disorders (IMD) according to pathogenic mechanisms[3,12,14-16,36]

Pathogenic mechanisms	Inherited metabolic disorders
Disorders of energy metabolism	Defective transport of various precursors of energy: GLUT1 deficiency, MCT1 defects Cytoplasmic energy defects: Defects in glycolysis, gluconeogenesis, and glycogen metabolism, Disorders of creatine metabolism Mitochondrial defects: Congenital lactic acidosis, Respiratory chain defects, Fatty acid oxidation disorders
Accumulation of neurotoxic substances/metabolites	Urea cycle defects, Disorders of amino acid metabolism, Disorders of organic acid metabolism, Disorders of purine and pyrimidine metabolism, Nonketotic hyperglycinemia, Sulfite oxidase deficiency, Accumulation of metal/minerals (Neurodegeration with brain iron accumulation, Wilson disease, Hypermanganesemia with dystonia)
Deficiencies of vitamins or cofactors	PDE, Pyridoxal 5'-phosphate dependent epilepsy, Folinic acid responsive epilepsy, Biotinidase deficiency, Methylene tetrahydrofolate reductase deficiency, Molybdenum cofactor deficiency, Sulfite oxidase deficiency
Impaired metallation and transport	Menkes disease
Impaired neuronal function due to accumulation of storage products	Storage disorders, Sialidosis type 1, Neuronal ceroid lipofuscinoses (NCL1, NCL2)
Disturbance of neurotransmitter systems	Nonketotic hyperglycinemia, Deficiency of GABA transaminase, Succinic semialdehyde dehydrogenase deficiency
Altered biophysical properties of cell membranes	GLUT1 deficiency, Smith-Lemli-Opitz syndrome
Dysfunction of intracellular organelles	Lysosomal disorders, Peroxisomal disorder
Associated brain malformations	Zellweger syndrome, Pyruvate dehydrogenase deficiency, Smith-Lemli-Opitz syndrome, Nonketotic hyperglycinemia, Sulfite oxidase deficiency

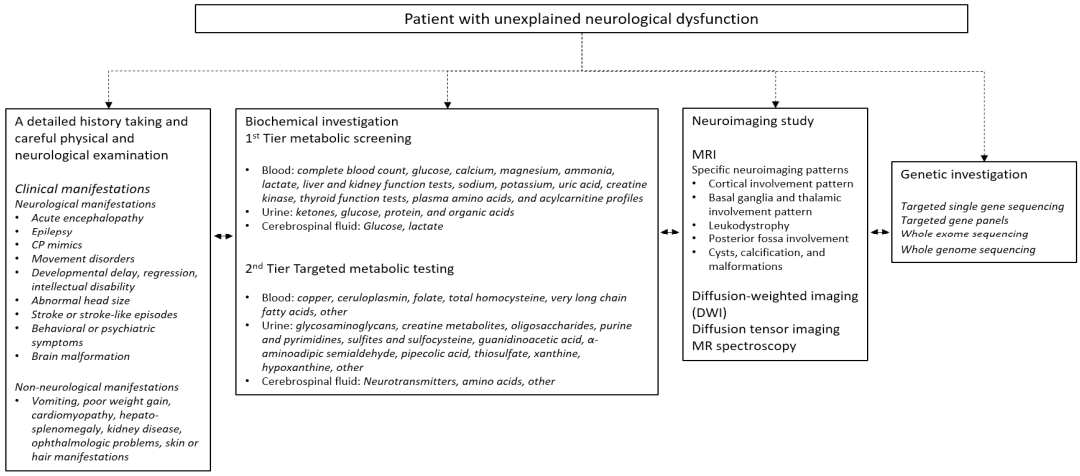

Fig. 1. Diagnostic approaches to neurometabolic disorders.

1. Clinical symptoms and signs

NMD present a variety of clinical manifestations, including prenatal-onset brain malformations, neonatal encephalopathy, and late-onset mild symptoms, depending on the impaired metabolic pathways. Unexplained acute illness, cardiomyopathy without heart anomaly, neonatal encephalopathy without hypoxic-ischemic injury, metabolic derangement including persistent hypoglycemia, elevated liver enzymes with coagulopathy, metabolic acidosis with increased anion gap, and severe ketoacidosis can be the clinical clues to IMD in the

neonatal period. Age of onset, type of onset, head circumference, certain neurological signs, typical facial appearance, cardiac, skeletal, renal, or hematologic abnormalities, ocular abnormalities, and skin problems may serve as important clinical information suggestive of a specific IMD[1-3].

2. Biochemical investigations

The initial work-up performed on children with suspected IMD includes metabolic screening of urine and blood. If necessary, this may include testing of cerebrospinal fluid (CSF). A blood sample is taken to measure complete blood count, glucose, calcium, magnesium, ammonia, lactate, liver and kidney function tests, sodium, potassium, uric acid, creatine kinase, thyroid function tests, plasma amino acids, and acylcarnitine profiles. Urine samples are analyzed for ketones, glucose, protein, and organic acids. Additional testing includes blood testing for specific metabolites suspected of IMD, including blood copper, ceruloplasmin, folate, plasma total homocysteine, plasma very long-chain fatty acid (VLCFA), and serum transferin isoelectric focusing[1-6].

According to the suspected IMD, urine testing for glycosaminoglycans, creatine metabolites, oligosaccharides, purine and pyrimidines, sulfites and sulfocysteine, guanidinoacetic acid, α-aminoadipic semialdehyde, pipecolic acid, thiosulfate, xanthine, or hypoxanthine is considered.

A cerebrospinal fluid (CSF) sample may also be used to measure glucose, lactate, or certain amino acids along with a blood sample. Depending on the clinical situation, additional CSF testing for specific metabolites may be considered[6-8].

Further investigation to identify specific IMD can be determined based on phenotypic databases, biochemical results, and neuroimaging findings[30]. Nowadays, expanded newborn screening has enabled rapid diagnosis of some IMD and prompt initiation of specific treatments, thereby altering the course of the disease[38].

3. Neuroimaging study

Neuroimaging plays an important role in differentiating IMD from other diseases. It may suggest a metabolic pathway derangement and is useful in making a specific diagnosis[1,3,5,13]. Magnetic resonance imaging (MRI) and advanced technologies play a key role in the diagnosis of IMD. Many IMD may present with nonspecific findings or even normal neuroimaging in the early stages. However, certain NMD may exhibit specific neuroimaging patterns due to the selective vulnerability of different structures to various insults[3]. Brain involvement patterns provide clues to possible underlying metabolic disorders. Cortical involvement (swelling, cytotoxic edema, atrophy, and malformations), basal ganglia and thalamic involvement (abnormal signal intensity, atrophy, dysplasia, calcifications, and metal deposition), leukodystrophy (hypomyelination, dysmyelination, and demyelination), and posterior fossa involvement as well as the presence of cysts, calcification, and malformations can help suspect and diagnose specific IMD[3].

Diffusion-weighted imaging (DWI) is useful in identifying areas of cytotoxic and intramyelinic edema and distinguishing them from areas of vasogenic edema, and is also useful in assessing disease activity[3]. Diffusion tensor imaging contributes to the identification and quantification of myelin damage even in the subclinical stage[3]. MR spectroscopy is useful for detecting abnormally increased or decreased metabolites, predicting disease progression, and monitoring treatment for specific NMD[3].

4. Genetic investigation

Most IMD ultimately require genetic investigation

to confirm the diagnosis, predict treatment response and prognosis, and estimate risk of recurrence. Genetic investigations can be performed, including single gene sequencing, targeted gene panels, whole exome or whole genome sequencing[13,39,40]. Targeted gene panels for specific IMD groups have enabled rapid and effective diagnosis, which is important for better treatment. Newborn genome sequencing for treatable conditions are also being studied[41].

Treatment

Treatment strategies for IMD depend on clinical manifestations and pathogenic mechanisms. It is important to provide a precise treatment approach based on the etiology and each specific symptom.

Some metabolic epilepsies and movement disorders associated with IMD can be treated according to their pathophysiology, including specific diets, supplements, medications, hematopoietic stem cell transplantation, and gene therapy (Table 3)[3,11,13,14,21].

When treating patients with IMD, it is advisable to regularly perform physical and neurological examinations in addition to disease-specific management during follow-up.

Conclusion

Early diagnosis of IMD is important because some disorders can be treated or improved with specific

Table 3. Treatable inherited metabolic disorders[3,11,13,14,21]

Inherited metabolic disorders	Treatment
Adrenoleukodystrophy	Allogeneic hematopoietic stem cell therapy (HSCT) Ex-vivo gene therapy
Arginase 1 deficiency	Protein restriction, Pegzilarginase
Ataxia with vitamin E deficiency	Vitamin E
Biotinidase deficiency	Biotin
Biotin-thiamine-responsive basal ganglia disease	Biotin, Thiamine
Cerebral creatine deficiency syndromes	Creatine monohydrate
Cerebral folate deficiency	Folinic acid
Cerebrotendinous xanthomatosis	Chenodeoxycholic acid
Cobalamin C deficiency	Cobalamin, betaine
Defects of serine biosynthesis	Serine, glycine
Disorders of CoQ10 biosynthesis	CoQ10
Dopa-responsive dystonia	Levodopa/carbidopa
Glucose transporter 1 (GLUT1) deficiency	Ketogenic diet
Glutaric aciduria type 1	Carnitine supplementation, Lysine restriction
Holocarboxylase synthetase deficiency	Biotin
Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome	Protein restriction, supplementation of citrulline and arginine
Maple syrup urine disease	Dietary restriction of branched chain amino acids
Menkes disease	Copper histidine
Ornithine transcarbamylase deficiency and other urea cycle defects	Dietary restriction of nitrogen and supplements to augment nitrogen disposal
Phenylketonuria (PKU)	Low-phenylalanine diet
Pyridoxal 5'-phosphate oxidase (PNPO) deficiency	Pyridoxal 5'-phosphate±pyridoxine
Pyridoxine dependent epilepsy	Pyridoxine±folinic acid
Pyruvate dehydrogenase deficiency	Ketogenic diet, thiamine
Vitamin E deficiency	Vitamin E replacement
Wilson disease	D-penicillamine, trientine, zinc

treatments. IMD should be considered in the differential diagnosis of patients of any age presenting with neurological symptoms. For prompt diagnosis and treatment, it is important to be familiar with the clinical characteristics, biochemical abnormalities, and characteristic neuroimaging patterns of specific IMD[40]. Relevant clinical, biochemical, and neuroimaging features may provide clues to the underlying diagnosis of IMD. Expanded newborn screening and next-generation sequencing technologies are also useful in diagnosing IMD[39-41].

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